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(54) **Substituted pyridylsulfinylbenzimidazoles having gastric acid secretion properties, pharmaceutical preparations containing same, and intermediates for their preparation.**

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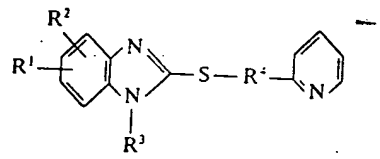
Substituted pyridylsulfinylbenzimidazoles having gastric acid secretion properties, pharmaceutical preparations containing same, and intermediates for their preparation

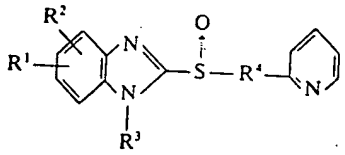
The present invention relates to new compounds having valuable properties in affecting gastric acid secretion in mammals, including man and pharmaceutical preparations containing said novel compounds, as well as intermediates for their preparation.

The object of the present invention is to obtain compounds which affect gastric acid secretion, and which inhibit exogenously or endogenously stimulated gastric acid secretion. These compounds can be used in the treatment of peptic ulcer disease.

It is previously known from DE-A 25 04 252 and 25 48 340 (AB HÄSSLE) that compounds of the formulas I and II



(I)

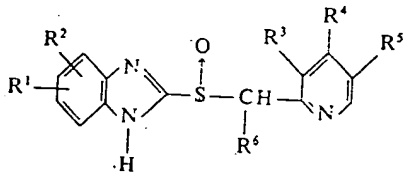


(II)

wherein R^1 and R^2 are each hydrogen, alkyl, halogen, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, carbamoyl, carbamoyloxy, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl or acyl in any position, R^3 is hydrogen, alkyl, acyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl, or alkylsulphonyl, and R^4 is straight or branched alkylene groups having 1 to 4 carbon atoms, whereby at most one methylene group is present between S and the pyridyl group, and whereby the pyridyl group may be further substituted with alkyl or halogen, posses inhibiting effect of gastric acid secretion.

It has now, however, surprisingly been found that the compounds defined below posses a still greater inhibiting effect than those given above.

Compounds of the invention are those of the general formula III



(III)

or a therapeutically acceptable salt thereof, wherein R^1 and R^2 are same or different and are each hydrogen, alkyl, halogen, methoxycarbonyl, ethoxycarbonyl, alkoxy, or alkanoyl, R^6 is hydrogen, methyl, or ethyl, and R^3, R^4 and R^5 are same or different and are each hydrogen, methyl, methoxy, ethoxy, methoxyethoxy or ethoxyethoxy, whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4 and R^5 is not methyl.

Alkyl R^1 and R^2 of formula III are suitably alkyl having up to 7 carbon atoms, preferably up to 4 carbon atoms. Thus, alkyl R may be methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl.

Halogen R^1 and R^2 is chloro, bromo, fluoro, or iodo.

Alkoxy R^1 and R^2 are suitably alkoxy groups having up to 5 carbon atoms, preferably up to 3 carbon atoms, as methoxy, ethoxy, n-propoxy, or isopropoxy.

Alkanoyl R^1 and R^2 have preferably up to 4 carbon atoms and are e. g. formyl, acetyl, or propionyl, preferably acetyl.

A preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each hydrogen, alkyl, methoxycarbonyl, alkoxy, or alkanoyl, whereby R^1 and R^2 are not both hydrogen, R^6 is hydrogen, and R^3, R^4, and R^5 are the same or different and are each hydrogen, methyl, methoxy, or ethoxy, whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4 and R^5 are hydrogen the third of R^3, R^4, and R^5 is not methyl.

A second preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each hydrogen, alkyl, halogen, methoxycarbonyl, ethoxycarbonyl, alkoxy, or alkanoyl, R^6 is hydrogen, methyl, or ethyl, R^3 is methyl, R^4 is methoxy, and R^5 is methyl.

A third preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each hydrogen, alkyl, halogen, methoxycarbonyl, ethoxycarbonyl, alkoxy, or alkanoyl, R^6 is hydrogen, methyl or ethyl, and R^3 is hydrogen, R^4 is methoxy and R^5 is methyl or R^3 is methyl, R^4 is methoxy and R^5 is hydrogen.

A fourth preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each hydrogen, alkyl, halogen, methoxycarbonyl, ethoxycarbonyl, alkoxy, or alkanoyl, R^6 is hydrogen, methyl or ethyl, R^3 and R^5 are hydrogen and R^4 is methoxy.

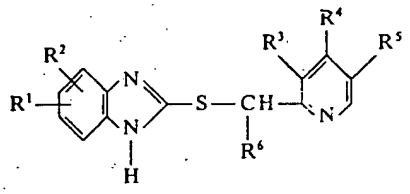
A fifth preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each hydrogen, alkyl, halogen, methoxycarbonyl, ethoxycarbonyl, alkoxy or alkanoyl, R^6 is hydrogen, methyl, or ethyl, and R^3 and R^5 are methyl, and R^4 is hydrogen.

A sixth preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each hydrogen, alkyl, halogen, methoxycarbonyl, ethoxycarbonyl, alkoxy, or alkanoyl, R^6 is hydrogen, methyl, or ethyl, R^3 and R^5 are hydrogen and R^4 is ethoxy, methoxyethoxy or ethoxyethoxy.

A seventh preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each hydrogen, alkyl, halogen, methoxycarbonyl, alkoxy, or alkanoyl, R^6 is hydrogen, methyl, or ethyl, R^3, R^4 and R^5 are all methyl.

Compounds of formula III above may be prepared according to the following methods:

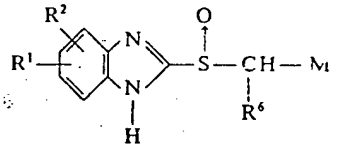
a) oxidizing a compound of formula IV



(IV)

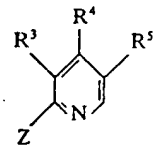
wherein R^1, R^2, R^6, R^3, R^4, and R^5 have the meanings given, to form a compound of formula III.

b) reacting a compound of the formula V



(V)

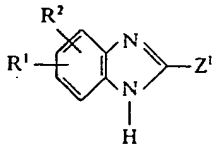
wherein R^1, R^2, and R^6 have the meanings given above and M is a metal selected from K, Na and Li, with a compound of formula VI.



(VI)

wherein R^3, R^4, and R^5 have the same meanings as given above. Z is a reactive esterified hydroxy group, to form a compound of formula III;

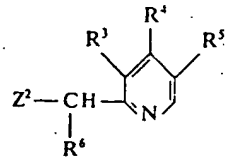
c) reacting a compound of the formula VII



(VII)

wherein R^1, and R^2 have the same meanings as given above and Z^1 is SH or a reactive esterified

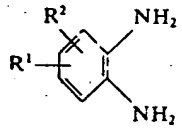
hydroxy group, with a compound of the formula VIII



(VIII)

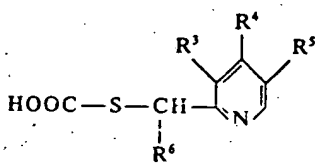
wherein R^6, R^3, R^4, and R^5 have the same meanings as given above, and Z^2 is a reactive esterified hydroxy group or SH, to form an intermediate of formula IV above, which then is oxidized to give a compound of formula III;

d) reacting a compound of the formula IX



(IX)

wherein R^1 and R^2 have the same meanings as given above with a compound of the formula X



(X)

wherein R^5, R^3, R^1 and R^5 have the same meanings as given above, to form an intermediate of formula IV above, which then is oxidized to give a compound of formula III, which compound may be converted to its therapeutically acceptable salts, if so desired.

In the reactions above, Z, Z^1, and Z^2 may be a reactive, esterified hydroxy group which is a hydroxy group esterified with strong, inorganic or organic acid, preferably a hydrohalogen acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, also sulfuric acid or a strong organic sulfonic acid as a strong aromatic acid, e. g. benzenesulfonic acid, 4-bromobenzenesulfonic acid or 4-toluenesulfonic acid.

The oxidation of the sulfur atom in the chains above to sulfinyl (S→O) takes place in the presence of an oxidizing agent as nitric acid, hydrogen peroxide, peracids, peresters, ozone, dinitrogentetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazobicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, ceric ammonium nitrate, bromine, chlorine, and sulfuryl chloride. The oxidation usually takes place in a solvent wherein the oxidizing agent is present in some excess in relation to the product to be oxidized.

Depending on the process conditions and the starting materials, the end product is obtained either as the free base or the acid addition salt, both of which are included within the scope of the invention. Thus, basic, neutral or mixed salts may be obtained as well as hemi, mono, sesqui or polyhydrates. The acid addition salts of the new compounds may in a manner known per se be transformed into free base using basic agents such as alkali or by ion exchange. On the other hand, the free bases obtained may form salts with organic or inorganic acids. In the preparation of acid addition salts preferably such acids are used which form suitable therapeutically acceptable salts. Such acids include hydrohalogen acids, sulfonic, phosphoric, nitric, and perchloric acids; aliphatic, alicyclic, aromatic, heterocyclic carboxy or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, antranilic, p-hydroxybenzoic, salicylic or p-aminosalicylic acid, embonic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogenbenzenesulfonic, toluenesulfonic, naphthylsulfonic or sulfanilic acids; methionine, tryptophane, lysine or arginine.

These or other salts of the new compounds, as e. g. picrates, may serve as purifying agents of the free bases obtained. Salts of the bases may be formed, separated from solution, and then the free base can be recovered from a new salt solution in a purer state. Because of the relationship between the new compounds in free base form and their salts, it will be understood that the corresponding salts are included within the scope of the invention.

Some of the new compounds may, depending on the choice of starting materials and process, be

present as optical isomers or racemates, or if they contain at least two asymmetric carbon atoms, be present as an isomer mixture (racemate mixture).

The isomer mixtures (racemate mixtures) obtained may be separated into two stereoisomeric (diastereomeric) pure racemates by means of chromatography or fractional crystallization.

The racemates obtained can be separated according to known methods, e. g. recrystallization from an optically active solvent, use of microorganisms, reactions with optically active acids forming salts which can be separated, separation based on different solubilities of the diastereomers. Suitable optically active acids are the L- and D-forms of tartaric acid, di-o-tolyl-tartaric acid, malic acid, mandelic acid, camphorsulfonic acid or quinic acid. Preferably the more active part of the two antipodes is isolated.

The starting materials are known or may, if they should be new, be obtained according to processes known per se.

In clinical use the compounds of the invention are administered orally, rectally or by injection in the form of a pharmaceutical preparation which contains an active component either as a free base or as a pharmaceutically acceptable, non-toxic acid addition salt, such as hydrochloride, lactate, acetate, sulfamate, in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semisolid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1 to 95% by weight of the preparation, between 0.5 to 20% by weight in preparations for injection and between 2 and 50% by weight in preparations for oral administration.

In the preparation of pharmaceutical preparations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with an anti-friction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed into tablets. If coated tablets are desired, the above prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating various dyes may be added in order to distinguish among tablets with different active compounds or with different amount of the active compound present.

Soft gelatin capsules may be prepared which capsules contain a mixture of the active compound or compounds of the invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier as lactose, saccarose, sorbitol mannitol, potato starch, corn starch, amylopectin cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance in a mixture with a neutral fat base, or they may be prepared in the form of gelatin-rectal capsules which contain the active substance in a mixture with a vegetable oil or paraffin oil.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e. g. solutions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar and a mixture of ethanol, water, glycerol and propylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharin and carboxymethylcellulose as a thickening agent.

Solutions for parenteral administration by injection may be prepared as an aqueous solution of a water soluble pharmaceutically acceptable salt of the active compound, preferably in a concentration from 0.5 to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different dosage unit ampoules.

Pharmaceutical tablets for oral use are prepared in the following manner: The solid substances are ground or sieved to a certain particle size, and the binding agent is homogenized and suspended in a suitable solvent. The therapeutically active compounds and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of approximately 1 mm. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, antifriction and antiadhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and its ability to dissolve in water. The compression pressure used should be in the range 0.5 to 5 tons. Tablets are manufactured at the rate of 20.000 to 200.000 per hour. The tablets, especially those which are rough or bitter, may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices. The different types of packages consist of glass or plastic gallipots, boxes, tubes and specific dosage adapted packages.

The typical daily dose of the active substance varies according to the individual needs and the manner of administration. In general, oral dosages range from 100 to 400 mg/day of active substance and intravenous dosages range from 5 to 20 mg/day.

The following illustrates preferred embodiments of the invention. Temperature is given in degrees Centigrades.

The starting materials in the examples found below were prepared in accordance with the following methods:

(1) a 1,2-diamino compound, such as o-phenylenediamine was reacted with potassium ethylxanthate (according to Org. Synth. Vol. 30, p. 56) to form a 2-mercaptobenzimidazole;
(2) the compound 2-chloromethylpyridine was prepared by reacting 2-hydroxymethylpyridine with thionylchloride (according to Arch. Pharm. Vol. 26, pp. 448—451 (1956));
(3) the compound 2-chloromethylbenzimidazole was prepared by condensing o-phenylenediamine with chloroacetic acid.

Example 1

28.9 g of 2-[2-(4,5-dimethyl-pyridyl)methylthio]-5-acetyl-6-methyl-benzimidazole were dissolved in 160 ml of $CHCl_3$, 24.4 g of m-chloroperbenzoic acid were added in portions while stirring and cooling to 5°C. After 10 minutes, the precipitated m-chlorobenzoic acid was filtered off. The filtrate was diluted with CH_2Cl_2, washed with Na_2CO_3 solution, dried over Na_2SO_4 and evaporated in vacuo. The residue crystallized when diluted with CH_3CN, and 2-[2-(4,5-dimethyl-pyridyl)methylsulfinyl]-5-acetyl-6-methyl-benzimidazole was recrystallized from CH_3CN. Yield 22.3 g; m. p. 158°C.

Examples 2—30

The preparation of compounds of formula III labelled 2—26 was carried out in accordance with Example 1 above. The compounds prepared are listed in Table 1 which identifies the substituents for these compounds.

Example 31 (method c)

0.1 moles of 4-6-dimethyl-2-mercaptobenzimidazole were dissolved in 20 ml of water and 200 ml of ethanol containing 0.2 moles of sodium hydroxide. 0.1 moles of 2-chloromethyl-(3,5-dimethyl)pyridine hydrochloride were added and the mixture was refluxed for two hours. The sodium chloride formed was filtered off and the solution was evaporated in vacuo. The residue was dissolved in acetone and was treated with active carbon. An equivalent amount of concentrated hydrochloric acid was added, whereupon the mono-hydrochloride of 2-[2-(3,5-dimethyl-pyridyl)-methylthio]-4,6-dimethyl-benzimidazole was isolated. Yield 0.05 moles.

This compound was then oxidized in accordance with Example 1 above to give the corresponding sulfinyl compound melting point 50—55°C.

Example 32 (method b)

0.1 moles of 2-[Li-methylsulfinyl]5-acetyl-6-methyl-benzimidazole were dissolved in 150 mls of benzene. 0.1 moles 2-chloro-(3,5-dimethyl)pyridine were added and the mixture was refluxed for two hours. The lithiumchloride formed was filtered off, and the solution was evaporated in vacuo. The residue was crystallized from CH_3CN, and recrystallized from the same solvent. Yield 0.82 moles of 2-[2-(3,5-dimethyl-pyridyl)methylsulfinyl]-5-acetyl-6-methyl-benzimidazole melting at 171°C.

Example 33 (method d)

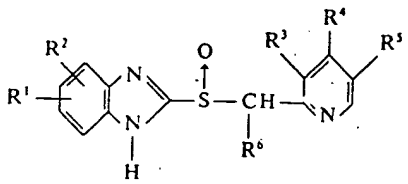
23.4 g of 2-[2-(3,4,5-trimethyl-pyridyl)methylthio]formic acid and 16.6 g of o-(5-acetyl-6-methyl)phenylenediamine were boiled for 40 minutes in 100 ml of 4N HCl. The mixture was cooled and neutralized with ammonia. The neutral solution was then extracted with ethyl acetate. The organic phase was treated with active carbon and evaporated in vacuo. The residue was dissolved in acetone whereupon an equivalent of concentrated HCl was added. The precipitated hydrochloride was filtered off after cooling and the salt was recrystallized from absolute ethanol and some ether. Yield of 2-[2-(3,4,5-trimethylpyridyl)methylthio]-5-acetyl-6-methyl-benzimidazole was 6.5 g.

This compound was then oxidized in accordance with Example 1 above, to give the corresponding sulfinyl derivative. M. p. 190°C.

Example 34 (method c)

22.0 g of 2-mercapto-5-acetyl-6-methyl-benzimidazole and 19.5 g of chloromethyl(4,5-dimethyl)pyridine hydrochloride were dissolved in 200 ml of 95% ethanol. 8 g of sodium hydroxide in 20 ml of water were added, whereupon the solution was refluxed for two hours. The sodium chloride formed was filtered off and the solution was evaporated in vacuo. The residue, 2-[2-(4,5-dimethyl-pyridyl)methylthio]-5-acetyl-6-methyl-benzimidazole, was recrystallized from 70% ethanol. Yield 10.6 g.

This compound was then oxidized in accordance with Example 1 above, to give the corresponding sulfinyl derivative, m. p. 158°C.



Ex.	R^1	R^2	R^6	R^3	R^4	R^5	M. p. °C
1	5-$COCH_3$	6-CH_3	H	H	CH_3	CH_3	158
2	5-$COOCH_3$	6-CH_3	H	H	CH_3	CH_3	163
3	5-$COOCH_3$	H	H	H	CH_3	CH_3	141
4	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	H	160
5	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	H	163
6	4-CH_3	6-CH_3	H	CH_3	H	CH_3	50–55
7	5-$COCH_3$	6-CH_3	H	CH_3	H	CH_3	171
8	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	190
9	5-$COCH_3$	6-CH_3	H	H	OCH_3	H	165
10	4-CH_3	6-CH_3	H	H	OCH_3	H	122
11	5-$COCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	156
12	5-$COOCH_3$	6-CH_3	H	CH_3	H	CH_3	144
13	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	185
14	5-$COOCH_3$	6-CH_3	H	H	OCH_3	H	169
15	5-$COOCH_3$	6-CH_3	H	H	OC_2H_5	H	148
16	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	H	175
17	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	155
18	5-$COOCH_3$	6-CH_3	H	H	OCH_3	CH_3	158
19	5-$COOCH_3$	H	H	CH_3	H	CH_3	141
20	5-$COOCH_3$	H	H	CH_3	OCH_3	CH_3	142
21	5-$COCH_3$	H	H	CH_3	OCH_3	CH_3	162
22	5-OCH_3	H	H	H	OCH_3	CH_3	178
23	5-OCH_3	H	H	CH_3	OCH_3	CH_3	156
24	5-CH_3	H	H	CH_3	OCH_3	CH_3	181
25	H	H	H	CH_3	OCH_3	CH_3	165
26	5-Cl	H	H	CH_3	OCH_3	CH_3	185
27	5-CH_3	H	H	H	$OC_2H_4OCH_3$	H	119
28	5-$COOC_2H_5$	H	H	CH_3	OCH_3	CH_3	150-5
29	5-$COOCH_3$	H	CH_3	CH_3	H	CH_3	130
30	5-CH_3	H	CH_3	CH_3	H	CH_3	152

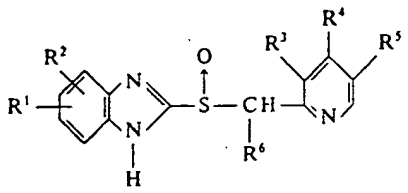
Biological effect

The compounds of the invention possess worthwhile therapeutic properties as gastric acid secretion inhibitors as demonstrated by the following tests. To determine the gastric acid secretion inhibitory properties, experiments have been performed in conscious dogs provided with gastric fistulas of conventional type and duodenal fistulas, the latter ones used for direct intraduodenal administation of the compounds. After 18 hours starvation and deprivation of water the dogs were given a subcutaneous infusion of pentagastrin (1—4 nmol/kg, h) lasting for 6—7 hours. Gastric juice was collected in consecutive 30 minutes samples. An aliquot of each sample was titrated with 0.1 N NaOH to pH = 7.0 for titrable acid concentration using an automatic titrator and pH-meter (Radiometer, Copenhagen, Denmark). Acid output was calculated as mmol H^+/60 minutes. The percent inhibition compared to control experiments was calculated for each compound and the peak inhibitory effect is given in Table 2 below. The test compounds, suspended in 0.5% Methocel[3] (registered Trade Mark for methyl cellulose), were given intraduodenally in doses from 4—20 µmol/kg when the secretory response to pentagastrin had reached a steady level.

In the test prior known compounds were compared with the compounds of the present invention as will be evident from the Table 2 below.

The following gastric acid inhibiting effect data were obtained for a number of compounds tested according to the method described.

Tabelle 2



Ex.	R^1	R^2	R^6	R^3	R^4	R^5	Dose µmol/kg	Effect % inhibition
1	5-$COCH_3$	6-CH_3	H	H	CH_3	CH_3	2	90
4	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	H	1	60
7	5-$COCH_3$	6-CH_3	H	CH_3	H	CH_3	2	100
8	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	4	100
9	5-$COCH_3$	6 CH_3	H	H	OCH_3	H	2	95
11	5-$COCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	0.5	70
*	5-$COCH_3$	6-CH_3	H	H	CH_3	H	20	30
*	5-$COCH_3$	6-CH_3	H	H	H	CH_3	8	80
2	5-$COOCH_3$	6-CH_3	H	H	CH_3	CH_3	2	60
5	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	H	2	90
12	5-$COOCH_3$	6-CH_3	H	CH_3	H	CH_3	2	70
13	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	4	80
14	5-$COOCH_3$	6-CH_3	H	H	OCH_3	H	2	100
15	5-$COOCH_3$	6-CH_3	H	H	OC_2H_5	H	4	75
16	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	H	0.5	65
17	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	0.5	90
18	5-$COOCH_3$	6-CH_3	H	H	OCH_3	CH_3		
*	5-$COOCH_3$	6-CH_3	H	H	H	CH_3	4	50
*	5-$COOCH_3$	6-CH_3	H	Br	H	H	4	0
6	4-CH_3	6-CH_3	H	CH_3	H	CH_3	4	40
10	4-CH_3	6-CH_3	H	H	OCH_3	H	2	40
*	4-CH_3	6-CH_3	H	H	H	H	4	30
*	4-CH_3	6-CH_3	H	H	H	CH_3	12	50
3	5-$COOCH_3$	H	H	H	CH_3	CH_3	4	100
19	5-$COOCH_3$	H	H	CH_3	H	CH_3	2	60
20	5-$COOCH_3$	H	H	CH_3	OCH_3	CH_3	0.5	65
*	5-$COOCH_3$	H	H	H	H	CH_3	20	90
*	5-$COOCH_3$	H	H	H	H	H	20	50
21	5-$COCH_3$	H	H	CH_3	OCH_3	CH_3	0.5	60
*	5-$COCH_3$	H	H	H	H	C_2H_5	20	40
22	5-OCH_3	H	H	H	OCH_3	CH_3		

(Continuation)

Ex.	R^1	R^2	R^6	R^3	R^4	R^5	Dose µmol/kg	Effect % inhibition
23	5-OCH_3	H	H	CH_3	OCH_3	CH_3	0.5	65
*	5-OCH_3	H	H	H	CH_3	H	20	10
24	5-CH_3	H	H	CH_3	OCH_3	CH_3	0.5	50
*	5-CH_3	H	H	H	H	CH_3	4	50
25	H	H	H	CH_3	OCH_3	CH_3	0.5	60
*	H	H	H	H	H	H	4	50
28	5-$COOC_2H_5$	H	H	CH_3	OCH_3	CH_3	0.5	50
26	5-Cl	H	H	CH_3	OCH_3	CH_3	0.5	25
27	5-CH_3	H	H	H	$OC_2H_4OCH_3$	H	0.5	30
29	5-$COOCH_3$	H	CH_3	CH_3	H	CH_3	0.5	40

*) Denotes a previously known compound (DE-A 25 04 252 and 25 48 340).

Example 35

A syrup containing 2% (weight per volume) of active substance was prepared from the following ingredients:

2-[2-(4,5-dimethyl-pyridyl)methylsulfinyl]-5-acetyl-6-methyl-benzimidazole · HCl	2.0 g
Saccharin	0.6 g
Sugar	30.0 g
Glycerin	5.0 g
Flavouring agent	0.1 g
Ethanol 96%	10.0 ml

Distilled water (sufficient to obtain a final volume of 100 ml)

Sugar, saccharin and the acid addition salt were dissolved in 60 g of warm water. After cooling, glycerin and a solution of flavouring agents dissolved in ethanol were added. To the mixture water was added to obtain a final volume of 100 ml.

The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

Example 36

2-[2-(3,4-dimethyl-pyridyl)methylsulfinyl]-5-acetyl-6-methyl-benzimidazole · HCl (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silicic acid (32 g). The mixture was moistened with 10% solution of gelatin and was ground through a 12-mesh sieve. After drying, potato starch (160 g), talc (50 g) and magnesium stearate (5 g) were added and the mixture thus obtained was pressed into tablets (10.000), with each tablet containing 25 mg of active substance. Tablets can be prepared that contain any desired amount of the active ingredient.

Example 37

Granules were prepared from 2-[2-(3,5-dimethyl-pyridyl)-methylsulfinyl]-5-acetyl-6-methyl-benzimidazole-p-hydroxybenzoate (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After drying, the granules were mixed with talc (25 g), potato starch (40 g), and magnesium stearate (2.50 g) and were pressed into 10.000 tablets. These tablets are first coated with a

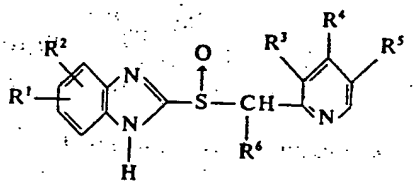
10% alcoholic solution of shellac and thereupon with an aqueous solution containing saccharose (45%), gum arabic (5%), gelatin (4%), and dyestuff (0.2%). Talc and powdered sugar were used for powdering after the first five coatings. The coating was then covered with a 66% sugar syrup and polished with a solution of 10% carnauba wax in carbon tetrachloride.

Example 38

2-[2-(3,5-dimethyl-pyridyl)methylsulfinyl]-5-acetyl-6-methyl-benzimidazole hydrochloride (1 g), sodium chloride (0.6 g) and ascorbic acid (0.1 g) were dissolved in sufficient amount of distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance for each ml, was used in filling ampoules, which were sterilized by heating at 120° C for 20 minutes.

Claims

1. A compound of formula III



(III)

or a therapeutically acceptable salt thereof in which R^1 and R^2 are the same or different and are hydrogen, alkyl, halogen, methoxycarbonyl, ethoxycarbonyl, alkoxy, or alkanoyl in any position, R^6 is hydrogen, methyl or ethyl, R^3, R^4 and R^5 are the same or different and are each hydrogen, methyl, methoxy, ethoxy, methoxyethoxy or ethoxyethoxy, whereby R^3, R^4, and R^5 and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 is not methyl.

2. A compound according to claim 1, which is

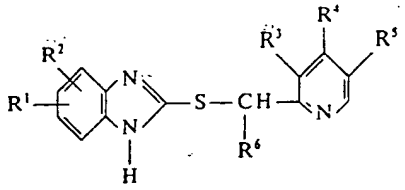
2-[2-(3,4-dimethyl-pyridyl)methylsulfinyl]-5-acetyl-6-methyl-benzimidazole,
2-[2-(3,5-dimethyl-pyridyl)methylsulfinyl]-4,6-dimethyl-benzimidazole,
2-[2-(4,5-dimethyl-pyridyl)methylsulfinyl]-5-methoxy-carbonyl-benzimidazole,
2-[2-(4,5-dimethyl-pyridyl)methylsulfinyl]-5-acetyl-6-methyl-benzimidazole,
2-[2-(4,5-dimethyl-pyridyl)methylsulfinyl]-5-methoxy-carbonyl-6-methyl-benzimidazole,
2-[2-(3,4-dimethyl-pyridyl)methylsulfinyl]-5-methoxy-carbonyl-6-methyl-benzimidazole,
2-[2-(3,5-dimethyl-pyridyl)methylsulfinyl]-5-acetyl-6-methyl-benzimidazole,
2-[2-(3,4,5-trimethyl-pyridyl)methylsulfinyl]-5-acetyl-6-methyl-benzimidazole,
2-[2-(4-methoxy-pyridyl)methylsulfinyl]-5-acetyl-6-methyl-benzimidazole,
2-[2-(4-methoxy-pyridyl)methylsulfinyl]-4,6-dimethyl-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy-pyridyl)methylsulfinyl]-5-acetyl-5-methyl-benzimidazole,
2-[2-(3,5-dimethyl-pyridyl)methylsulfinyl]-5-methoxy-carbonyl-6-methyl-benzimidazole,
2-[2-(3,4,5-trimethyl-pyridyl)methylsulfinyl-5-methoxy-carbonyl-6-methyl-benzimidazole,
2-[2-(4-methoxy-pyridyl)methylsulfinyl]-5-methoxycarbonyl-6-methyl-benzimidazole,
2-[2-(4-ethoxy-pyridyl)methylsulfinyl]-5-methoxycarbonyl-6-methyl-benzimidazole,
2-[2-(3-methyl-4-methoxy-pyridyl)methylsulfinyl]-5-methoxycarbonyl-6-methyl-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy-pyridyl)methylsulfinyl]-5-methoxycarbonyl-6-methyl-benzimidazole,
2-[2-(4-methoxy-5-methyl-pyridyl)methylsulfinyl]-5-methoxycarbonyl-6-methyl-benzimidazole,
2-[2-(3,5-dimethyl-pyridyl)methylsulfinyl]-5-methoxycarbonyl-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy-pyridyl)methylsulfinyl]-5-methoxycarbonyl-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy-pyridyl)methylsulfinyl]-5-acetyl-benzimidazole,
2-[2-(4-methoxy-5-methyl-pyridyl)methylsulfinyl]-5-methoxy-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy-pyridyl)methylsulfinyl]-5-methoxy-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy-pyridyl)methylsulfinyl]-5-methyl-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy-pyridyl)methylsulfinyl]-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy-pyridyl)methylsulfinyl]-5-chloro-benzimidazole

3. A pharmaceutical preparation for inhibiting gastric acid secretion, characterized in that it contains as active agent a compound according to claim 1 or a pharmaceutically acceptable non-toxic acid

addition salt thereof in a therapeutically effective amount in combination with a pharmaceutically acceptable carrier.

4. A pharmaceutical preparation according to claim 3 wherein the active ingredient is one of the compounds according to claim 2.

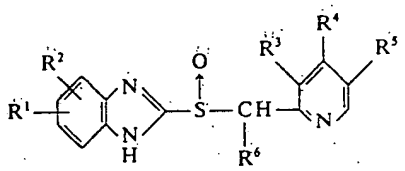
5. Intermediates of the formula



wherein R^1, R^2, R^3, R^4, R^5 and R^6 are defined according to claim 1.

Patentansprüche

1. Verbindung der Formel III



(III)

oder ein therapeutisch verträgliches Salz derselben, worin R^1 und R^2 gleich oder verschieden sind und ein Wasserstoffatom, eine Alkylgruppe, ein Halogenatom, eine Methoxycarbonylgruppe, eine Äthoxycarbonylgruppe, eine Alkoxygruppe oder eine Alkanoylgruppe in irgendeiner Stellung bedeuten, R^6 ein Wasserstoffatom eine Methylgruppe oder eine Äthylgruppe bedeutet, R^3, R^4 und R^5 gleich oder verschieden sind und jeweils ein Wasserstoffatom, eine Methylgruppe, eine Methoxygruppe, eine Äthoxygruppe, eine Methoxyäthoxygruppe oder eine Äthoxyäthoxygruppe bedeuten, wobei R^3, R^4 und R^5 nicht alle ein Wasserstoff bedeuten und wobei, wenn zwei der Substituenten R^3, R^4 und R^5 Wasserstoffatome sind, der dritte Substituent von R^3, R^4 und R^5 keine Methylgruppe ist.

2. Verbindung nach Anspruch 1, die

2-[2-(3,4-Dimethylpyridyl)-methylsulfinyl]-5-acetyl-6-methylbenzimidazol,
2-[2-(3,5-Dimethylpyridyl)-methylsulfinyl]-4,6-dimethylbenzimidazol,
2-[2-(4,5-Dimethylpyridyl)-methylsulfinyl]-5-methoxycarbonylbenzimidazol,
2-[2-(4,5-Dimethylpyridyl)-methylsulfinyl]-5-acetyl-6-methylbenzimidazol,
2-[2-(4,5-Dimethylpyridyl)-methylsulfinyl]-5-methoxycarbonyl-6-methylbenzimidazol,
2-[2-(3,4-Dimethylpyridyl)-methylsulfinyl]-5-methoxycarbonyl-6-methylbenzimidazol,
2-[2-(3,5-Dimethylpyridyl)-methylsulfinyl]-5-acetyl-6-methylbenzimidazol,
2-[2-(3,4,5-Trimethylpyridyl)-methylsulfinyl]-5-acetyl-6-methylbenzimidazol,
2-[2-(4-Methoxypyridyl)-methylsulfinyl]-5-acetyl-6-methylbenzimidazol,
2-[2-(4-Methoxypyridyl)-methylsulfinyl]-4,5-dimethylbenzimidazol,
2-[2-(3,5-Dimethyl-4-methoxypyridyl)-methylsulfinyl]-5-acetyl-6-methylbenzimidazol,
2-[2-(3,5-Dimethylpyridyl)-methylsulfinyl]-5-methoxycarbonyl-6-methylbenzimidazol,
2-[2-(3,4,5-Trimethylpyridyl)-methylsulfinyl]-5-methoxycarbonyl-6-methylbenzimidazol,
2-[2-(Methoxypyridyl)-methylsulfinyl]-5-methoxycarbonyl-6-methylbenzimidazol,
2-[2-(4-Äthoxypyridyl)-methylsulfinyl]-5-methoxycarbonyl-6-methylbenzimidazol,
2-[2-(3-Methyl-4-methoxypyridyl)-methylsulfinyl]-5-methoxycarbonyl-6-methylbenzimidazol,
2-[2-(3,5-Dimethyl-4-methoxypyridyl)-methylsulfinyl]-5-methoxycarbonyl-6-methylbenzimidazol,
2-[2-(4-Methoxy-5-methylpyridyl)-methylsulfinyl]-5-methoxycarbonyl-6-methylbenzimidazol,
2-[2-(3,5-Dimethylpyridyl)-methylsulfinyl]-5-methoxycarbonylbenzimidazol,
2-[2-(3,5-Dimethyl-4-methoxypyridyl)-methylsulfinyl]-5-methoxycarbonylbenzimidazol,
2-[2-(3,5-Dimethyl-4-methoxypyridyl)-methylsulfinyl]-5-acetylbenzimidazol,
2-[2-(4-Methoxy-5-methylpyridyl)-methylsulfinyl]-5-methoxybenzimidazol,
2-[2-(3,5-Dimethyl-4-methoxypyridyl)-methylsulfinyl]-5-methoxybenzimidazol,
2-[2-(3,5-Dimethyl-4-methoxypyridyl)-methylsulfinyl]-5-methylbenzimidazol,

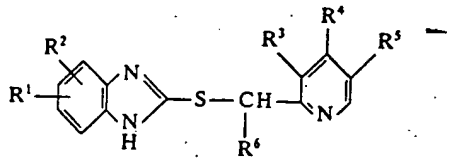
2-[2-(3,5-Dimethyl-4-methoxypyridyl)-methylsulfinyl]-benzimidazol,
2-[2-(3,5-Dimethyl-4-methoxypyridyl)-methylsulfinyl]-5-chlorbenzimidazol

ist.

3. Pharmazeutisches Präparat zur Hemmung der Magensäuresekretion, dadurch gekennzeichnet, daß es als aktives Mittel eine Verbindung gemäß Anspruch 1 enthält.

4. Pharmazeutisches Präparat nach Anspruch 3, worin der aktive Bestandteil eine der Verbindungen gemäß Anspruch 2 ist.

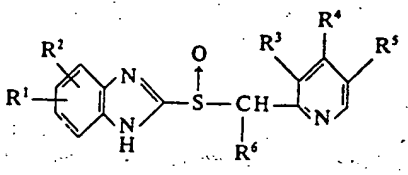
5. Zwischenprodukte der Formel



worin R^1, R^2, R^3, R^4, R^5 und R^6 gemäß Anspruch 1 definiert sind.

Revendications

1. Composé de la formule III



(III)

ou un sel thérapeutiquement acceptable de celui-ci, formule dans laquelle R^1 et R^2 sont semblables ou différents et sont un atome d'hydrogène, un groupe alkyle, un atome d'halogène, un groupe méthoxycarbonyle, éthoxycarbonyle, alcoxy ou alcanoyle dans toute position, R^6 est un atome d'hydrogène ou un groupe méthyle ou éthyle et R^3, R^4 et R^5 sont semblables ou différents et sont chacun un atome d'hydrogène ou un groupe méthyle, méthoxy, éthoxy, méthoxyéthoxy ou éthoxyéthoxy sous cette réserve que R^3, R^4 et R^5 ne sont pas tous des atomes d'hydrogène et que, lorsque deux des substituants R^3, R^4 et R^5 sont des atomes d'hydrogène, le troisième des substituants R^3, R^4 et R^5 n'est pas un groupe méthyle.

2. Composé selon la revendication 1, qui est

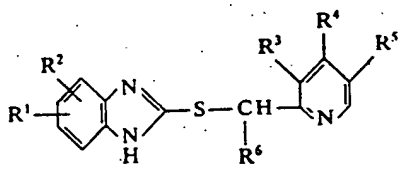
le 2-[2-(3,4-diméthyl-pyridyl)méthylsulfinyl]-5-acétyl-6-méthyl-benzimidazole,
le 2-[2-(3,5-diméthyl-pyridyl)méthylsulfinyl]-4,6-diméthylbenzimidazole,
le 2-[2-(4,5-diméthyl-pyridyl)méthylsulfinyl]-5-méthoxycarbonyl-benzimidazole,
le 2-[2-(4,5-diméthyl-pyridyl)méthyl-pyridyl)méthylsulfinyl]-5-acétyl-6-méthyl-benzimidazole,
le 2-[2-(4,5-diméthyl-pyridyl)méthylsulfinyl]-5-méthoxycarbonyl-6-méthyl-benzimidazole,
le 2-[2-(3,4-diméthyl-pyridyl)méthylsulfinyl]-5-méthoxycarbonyl-6-méthyl-benzimidazole,
le 2-[2-(3,5-diméthyl-pyridyl)méthylsulfinyl]-5-acétyl-6-méthyl-benzimidazole,
le 2-[2-(3,4,5-triméthyl-pyridyl)méthylsulfinyl]-5-acétyl-6-méthyl-benzimidazole,
le 2-[2-(4-méthoxy-pyridyl)méthylsulfinyl]-5-acétyl-6-méthyl-benzimidazole,
le 2-[2-(4-méthoxy-pyridyl)méthylsulfinyl]-4,6-diméthylbenzimidazole,
le 2-[2-(3,5-diméthyl-4-méthoxy-pyridyl)méthylsulfinyl]-5-acétyl-6-méthyl-benzimidazole,
le 2-[2-(3,5-diméthyl-pyridyl)méthylsulfinyl]-5-méthoxycarbonyl-6-méthyl-benzimidazole,
le 2-[2-(3,4,5-triméthyl-pyridyl)méthylsulfinyl]-5-méthoxycarbonyl-6-méthyl-benzimidazole,
le 2-[2-(4-méthoxy-pyridyl)méthylsulfinyl]-5-méthoxycarbonyl-6-méthyl-benzimidazole,
le 2-[2-(4-éthoxy-pyridyl)méthylsulfinyl]-5-méthoxycarbonyl-6-méthyl-benzimidazole,
le 2-[2-(3-méthyl-4-méthoxy-pyridyl)méthylsulfinyl]-5-méthoxycarbonyl-6-méthyl-benzimidazole,
le 2-[2-(3,5-diméthyl-4-méthoxy-pyridyl)méthylsulfinyl]-5-méthoxycarbonyl-6-méthyl-benzimidazole,
le 2-[2-(4-méthoxy-5-méthyl-pyridyl)méthylsulfinyl]-5-méthoxycarbonyl-6-méthyl-benzimidazole,
le 2-[2-(3,5-diméthyl-pyridyl)méthylsulfinyl]-5-méthoxycarbonyl-benzimidazole,
le 2-[2-(3,5-diméthyl-4-méthoxy-pyridyl)méthylsulfinyl]-5-méthoxycarbonyl-benzimidazole,
le 2-[2-(3,5-diméthyl-4-méthoxy-pyridyl)méthylsulfinyl]-5-acétyl-benzimidazole,

le 2-[2-(4-méthoxy-5-méthyl-pyridyl)méthylsulfinyl]-5-méthoxy-benzimidazole,
le 2-[2-(3,5-diméthyl-4-méthoxy-pyridyl)méthylsulfinyl]-5-méthoxy-benzimidazole,
le 2-[2-(3,5-diméthyl-4-méthoxy-pyridyl)méthylsulfinyl]-5-méthyl-benzimidazole,
le 2-[2-(3,5-diméthyl-4-méthoxy-pyridyl)méthylsulfinyl]-benzimidazole,
et le 2-[2-(3,5-diméthyl-4-méthoxy-pyridyl)méthylsulfinyl]-5-chloro-benzimidazole.

3. Composition pharmaceutique servant à inhiber la sécrétion d'acide gastrique, caractérisée en ce qu'elle contient comme agent actif un composé selon la revendication 1 ou un sel d'addition d'acide de celui-ci, non toxique, pharmaceutiquement acceptable selon une quantité thérapeutiquement efficace en combinaison avec un véhicule pharmaceutiquement acceptable.

4. Composition pharmaceutique selon la revendication 3, caractérisée en ce que l'ingrédient actif est l'un des composés selon la revendication 2.

5. Intermédiaires répondant à la formule:



dans laquelle R^1, R^2, R^3, R^4, R^5 et R^6 répondent à la définition donnée à la revendication 1.